EXHIBIT A

Pending Claims- U.S. Application Serial No. 10/690,389, filed October 21, 2003.
DDK docket No. 200.1030CON3

Claim 25. A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean fasting plasma concentration vs. time curve of Figure
14 upon single administration to human subjects.

Claim 26. A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean fed plasma concentration vs. time curve of Figure
14 upon single administration to human subjects.

Claim 27. A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean fasting plasma concentration vs. time curve of Figure
15 upon single administration to human subjects.

Claim 28. (new) A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean fed plasma concentration vs. time curve of Figure
15 upon single administration to human subjects.

Claim 29. A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean plasma concentration vs. time curve of Figure
16 upon steady state administration to human subjects.

Claim 30. A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean fasting plasma concentration vs. time curve of Figure
17 upon single administration to human subjects.

Claim 31. (new) A sustained release oral dosage form comprising:
hydromorphone or a pharmaceutically acceptable salt thereof; and
means for providing the mean fed plasma concentration vs. time curve of Figure
17 upon single administration to human subjects.

Pending Claims U.S. Application Serial No. 09/777,616, filed February 6, 2001.
DDK docket 200.1030CON2

Claim 1. A sustained-release pharmaceutical formulation comprising an extruded blend of a therapeutically active agent, one or more hydrophobic materials selected from the group consisting of alkylcelluloses, acrylic polymers, and mixtures thereof; and one or more hydrophobic fusible carriers having a melting point from about 30° to about 200 ° C and selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof, said extruded blend divided into a unit dose containing an effective amount of said therapeutically active agent to render a desired therapeutic effect and providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours, said extruded blend being formed by mixing the therapeutically active agent, the one or more hydrophobic materials, and the one or more hydrophobic fusible carriers in an extruder to form said blend and extruding said blend through the extruder.

Claim 2. The formulation of claim 1, wherein said extrudate comprises a strand shaped matrix cut into multi-particulates having a length of from about 0.1 to about 5 mm in length.

Claim 3. The formulation of claim 1, wherein said exrudate has a diameter of from about 0.1 to about 5mm.

Claim 4. The formulation of claim 1, wherein said therapeutically active agent is an opioid analgesic or a pharmaceutically acceptable salt thereof.

Claim 5. The formulation of claim 4, wherein said opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, bupernorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dexocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl, butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 6. The extrudate of claim 5 wherein said opioid analgesic is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, tramadol, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 7. The formulation of claim 2, wherein a unit dose comprising an effective amount of said multiparticulates to render a therapeutic effect is contained within a gelatin capsule.

Claim 8. The formulation of claim 2, wherein a unit dose comprising an effective amount of said multiparticluates to render a therapeutic effect is compressed into a tablet.

Claim 9. The formulation of claim 8, wherein said therapeutically active agent is tramadol or a pharmaceutically acceptable salt thereof.

Claim 10. The formulation of claim 7 wherein said therapeutically active agent is an opioid analgesic selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, tramadol, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 11. The formulation of claim 10, which provides an in-vitro release (when assesed by the USP Paddle or Basket Method at 100 prm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37 °C from about 1 to about 42.5% opioid released after one hour, from about 5 to about 65% opioid released after 2 hours, from about 15 to about 85% opioid released after 4 hours, from about 20 to about 90% opioid released after 6 hours, from about 35 to about 95% opioid released after 12 hours, from about 45 to about 100% opioid released after 18 hours, and from about 55 to about 100% opioid released after 24 hours, by weight.

Claim 12. The formulation of claim 10 which provides a peak plasma level at from about 2 to about 8 hours after oral administration.

Claim 13. The formulation of claim 10, which provides a W_{50} from about 4 to about 12 hours.

Claim 14. The formulation of claim 10, which provides a rapid rate of initial rise in the plasma concentration of the opioid after oral administration, such that the peak plasma level obtained in-vivo occurs from about 2 to about 8 hours after oral administration.

Claim 15. The formulation of claim 10, which provides a rapid rate of initial rise in the plasma concentration of the opioid after oral administration, such that the absorption half-life is from about 1 to about 8 hours after oral administration (in the fasted state).

Claim 16. The formulation of claim 10, which provides an in-vitro release (when assesed by the USP Paddle or Basket Method at 100 prm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37 °C from about 12.5 to about 42.5% opioid released after one hour, from about 25 to about 65% opioid released after 2 hours, from about 45 to about 85% opioid released after 4 hours, and greater than about 60% opioid released after 8 hours, by weight.

[redacted]

Claim 18. A method of preparing a sustained-release pharmaceutical extrudate suitable for oral administration, comprising:

blending in an extruder, a therapeutically active agent together with (1) a hydrophobic material selected from the group consisting of alkylcelluloses, acrylic polymers, and mixtures thereof and (2) a hydrophobic fusible carrier selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof, said retardant material having a melting point between 30-200° C and being included in an amount sufficient to further slow the release of the therapeutically active agent,

heating said blend to a temperature sufficient to soften the mixture sufficiently to extrude the same;

extruding said heated mixture as a strand having a diameter of from 0.1-3 mm;

cooling said strand; and

dividing said strand to form non-spheroidal multi-particulates of said extrudate having a length from 0.1-5 mm; and

dividing said non-spheroidal multi-particulates into unit doses containing an effective amount of said therapeutically active agent, said unit dose providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

Claim 19. The method of claim 18, wherein said therapeutically active agent is an opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, bupernorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dexocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, pharmaceutically acceptable salts thereof and mixtures thereof.

Claim 20. The method of claim 18, further comprising containing said unit dose of said multiparticulates within a gelatin capsule.

[redacted]

Claim 25. The formulation of claim 1, further comprising a plasticizer.

Claim 26. The formulation of claim 1, further comprising a lubricant.

Claim 27. The formulation of claim 25, wherein said plasticizer is selected from the group consisting of diethyl phthalate, tributyl citrate, triacetin, and mixtures thereof.

Claim 28. The formulation of claim 26, wherein said lubricant is selected from the group consisting of magnesium stearate, stearic acid, talc, and mixtures thereof.

Claim 29. The dosage form of claim 6, wherein said opioid analgesic is hydromorphone or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 4 mg to about 64 mg of hydromorphone or a pharmaceutically acceptable salt thereof.

Claim 30. The dosage form of claim 6, wherein said opioid analgesic is morphine or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 5 mg to about 800 mg of morphine or a pharmaceutically acceptable salt thereof.

Claim 31. The dosage form of claim 6, wherein said opioid analgesic is oxycodone or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 5 mg to about 400 mg of oxycodone or a pharmaceutically acceptable salt thereof.

Claim 32. The method of claim 18, further comprising blending a plasticizer with said therapeutically active agent, said hydrophobic material, and said hydrophobic fusible carrier prior to heating said blend.

Claim 33. The method of claim 32, wherein said plasticizer is selected from the group consisting of diethyl phthalate, tributyl citrate, triacetin, and mixtures thereof.

Claim 34. The method of claim 19, wherein said opioid analgesic is hydromoprhone or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 4 mg to about 64 mg of hydromorphone or a pharmaceutically acceptable salt thereof.

Claim 35. The method of claim 19, wherein said opioid analgesic is morphine or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 5 mg to about 800 mg of morphine or a pharmaceutically acceptable salt thereof.

Claim 36. The method of claim 19, wherein said opioid analgesic is oxycodone or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 5 mg to about

400 mg of oxycodone or a pharmaceutically acceptable salt thereof.

Claim 39. The formulation of claim 37, wherein said plasticizer is selected from the group consisting of diethyl phthalate, tributyl citrate, triacetin, and mixtures thereof.

Claim 40. The formulation of claim 38, wherein said lubricant is selected from the group consisting of magnesium stearate, stearic acid, talc, and mixtures thereof.

Claim 41. The dosage form of claim ~~4~~ 6, wherein said opioid analgesic is hydromorphone or a pharmaceutically acceptable salt thereof and the unit dose comprises from about 4 mg to about 64 mg of hydromorphone or a pharmaceutically acceptable salt thereof.

Claim 42. The dosage form of claim ~~4~~ 6, wherein said opioid analgesic is morphine or a pharmaceutically acceptable salt thereof and wherein said unit dose comprises from about 5 mg to about 800 mg of morphine or a pharmaceutically acceptable salt thereof.

Claim 43. The dosage form of claim ~~4~~ 6, wherein said opioid analgesic is oxycodone or a pharmaceutically acceptable salt thereof and wherein said unit dose comprises from about 5 mg to about 400 mg of oxycodone or a pharmaceutically acceptable salt thereof.

Pending Claims U.S. Application Serial No. 10/392,586, filed March 20, 2003.
DDK docket 200.94569CON2

15. A method of preparing a multiparticulate sustained release oral dosage form, comprising:

(a) mixing together a therapeutically active agent, a water-insoluble retardant, and an optional binder to obtain a homogeneous mixture, the ratio of said water insoluble retardant to said therapeutically active agent in said mixture being sufficient to impart a release of said therapeutically active agent from said particles over a time period of at least about 4 hours when said particle is exposed to an aqueous fluid;

(b) heating said homogenous mixture;

(c) extruding said homogeneous mixture to thereby form strands;

(d) cooling said strands containing said homogeneous mixture; and

(e) cutting said strands into particles having a size from about 0.1 mm to about 12 mm; and

(f) dividing said particles into unit doses.

16. The method of claim 15, wherein said unit doses are placed into gelatin capsules.

17. The method of claim 15, wherein said homogeneous mixture is heated to a temperature from about 30°C to about 200°C prior to extrusion.

18. The method of claim 15, wherein said therapeutically active agent is selected from the group consisting of systematically active therapeutic agents, locally active therapeutic agents, disinfecting agents, chemical impregnants, cleansing agents, deodorants, fragrances, dyes, animal repellents, insect repellents, a fertilizing agents, pesticides, herbicides, fungicides, and plant growth stimulants.

20. The unit dose of claim 18, wherein said therapeutically active agent is an opioid analgesic selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine,

ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metophon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.

24. The method of claim 15, wherein said retardant is selected from the group consisting of acrylic polymers, hydroxyalkylcelluloses and mixtures thereof.

25. The method of claim 15, wherein said acrylic polymer is comprised of monomers selected from the group consisting of an ester of acrylic acid, an ester of methacrylic acid, an alkyl ester of acrylic acid, an alkyl ester of methacrylic acid, and mixtures of any of the foregoing.

26. The method of claim 15, wherein said water insoluble binder is selected from the group consisting of hydrogenated vegetable or castor oil, paraffin, higher aliphatic alcohols, higher aliphatic acids, long chain fatty acids, fatty acid esters, and mixtures thereof.

27. The method of claim 15, wherein said binder is selected from the group consisting of higher aliphatic alcohols and water-insoluble waxes.

28. The method of claim 15, further comprising adjusting the aperture and aperture shape of the extruder to obtain a strand having a diameter from about 0.1 mm to about 3 cm.

29. A sustained release unit dose formulation comprising the particles prepared according to the method of claim15.

30. A method of treating a patient with a sustained release multiparticulate formulation of a therapeutically active agent, comprising:

(a) mixing together a therapeutically active agent, a water-insolube retardant, and an optional binder to obtain a homogeneous mixture, the ratio of said water insoluble retardant to said therapeutically active agent in said mixture being sufficient to impart a release of said therapeutically active agent from said particles over a time period of at least about 4 hours when said particle is exposed to an aqueous fluid;

(b) heating said homogeneous mixture;

(c) extruding said homogeneous mixture to thereby form strands;

(d) cooling said strands containing said homogeneous mixture; and

(e) cutting said strands into particles having a size from about 0.1 mm to about 12 mm;

(f) dividing said particles into unit doses; and

(g) administering said unit dose to a patient.

31. A method of preparing a multiparticulate sustained release oral dosage form, comprising:

(a) directly metering into an extruder a water-insoluble retardant, a therapeutically active agent, and an optional binder;

(b) heating said homogeneous mixture;

(c) extruding said homogeneous mixture to thereby form strands;

(d) cooling said strands containing said homogeneous mixture; and

(e) cutting said strands into particles having a size from about 0.1 mm to about 12 mm; and

(f) dividing said particles into unit doses.

32. The unit dose of claim 1, wherein the diameter of said particles is from about 0.1 mm to about 3 cm.

33. The dosage form of claim 1, wherein said therapeutically active agent is an opioid and said retardant is an acrylic polymer.

34. The dosage form of claim 1, wherein said therapeutically active agent is an opioid and said retardant is a hydroxyalkylcellulose.

35. An opioid unit dose sustained-release oral dosage form having substantially no feeding-fasting effect, comprising a plurality of melt extruded particles, each of said particles comprising:

(a) a therapeutically active agent;

(b) one or more retardants; and

(c) an optional water insoluble binder;

said particles having a (length) size from about 0.1 mm to about 12 mm, said unit dose providing a release of said therapeutically active agent over at least about 12-24 hours.

36. An opioid unit dose sustained-release oral dosage form having substantially no feeding-fasting effect, comprising a plurality of melt extruded particles, each of said particles comprising:

(a) a therapeutically active agent;

(b) one or more retardants; and

(c) an optional water insoluble binder;

said particles having a (length) size from about 0.1 mm to about 12 mm, said unit dose providing a release of said therapeutically active agent over at least about 6 hours.

37. The dosage form of claim 35, wherein said therapeutically active agent is an opioid and said retardant is an acrylic polymer.

38. The dosage form of claim 36, wherein said therapeutically active agent is an opioid and said retardant is a hydroxyalkylcellulose.

39. A unit dose sustained-release oral dosage form comprising a plurality of melt extruded particles, each of said particles comprising:

(a) an opioid analgesic selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine,

dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metophon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof;

(b) one or more retardants; and

(c) an optional water insoluble binder,

said particles having a (length) size from about 0.1 mm to about 12 mm, said unit dose providing a release of said opioid analgesic over at least about 6 hours.

40. The unit dose of claim 39, wherein said opioid analgesic is morphine or

pharmaceutically acceptable salts thereof.

41. The unit dose of claim 39, wherein said opioid analgesic is codeine or pharmaceutically acceptable salts thereof.

42. The unit dose of claim 39, wherein said opioid analgesic is hydromorphone or pharmaceutically acceptable salts thereof.

43. The unit dose of claim 39, wherein said opioid analgesic is hydrocodone or pharmaceutically acceptable salts thereof.

44. The unit dose of claim 39, wherein said opioid analgesic is oxycodone or pharmaceutically acceptable salts thereof.

45. The unit dose of claim 39, wherein said retardant is selected from the group consisting of acrylic polymers, hydroxyalkylcelluloses and mixtures thereof.

46. The unit dose of claim 39, wherein said acrylic polymer is comprised of monomers selected from the group consisting of an ester of acrylic acid, an ester of methacrylic acid, an alkyl ester of acrylic acid, an alkyl ester of methacrylic acid, and mixtures of any of the foregoing.

47. The unit dose of claim 39, wherein said water insoluble binder is selected from the group consisting of hydrogenated vegetable or castor oil, paraffin, higher aliphatic alcohols, higher aliphatic acids, long chain fatty acids, fatty acid esters, and mixtures thereof.

48. The unit dose of claim 39, wherein said binder is selected from the group consisting of higher aliphatic alcohols and water-insoluble waxes.

49. The unit dose of claim 39, wherein said particles have a diameter from about 0.1 to about 5mm.

50. The unit dose of claim 39, wherein each of said particles comprise from about 1% to about 99% of said retardant.

51. The unit dose of claim 39, wherein each of said particles comprise from about 5% to about 95% of said retardant.

52. The unit dose of claim 20, wherein said opioid analgesic is morphine or pharmaceutically acceptable salts thereof.

53. The unit dose of claim 20, wherein said opioid analgesic is codeine or pharmaceutically acceptable salts thereof.

54. The unit dose of claim 20, wherein said opioid analgesic is hydromorphone or pharmaceutically acceptable salts thereof.

55. The unit dose of claim 20, wherein said opioid analgesic is hydrocodone or pharmaceutically acceptable salts thereof.

56. The unit dose of claim 20, wherein said opioid analgesic is oxycodone or pharmaceutically acceptable salts thereof.

57. A unit dose sustained-release oral dosage form comprising a plurality of melt extruded particles, each of said particles comprising:

(a) an opioid analgesic;

(b) one or more retardants; and

(c) an optional water insoluble binder;

said particles having a (length) size from about 0.1 mm to about 12 mm, said unit dose providing a release of said opioid analgesic over at least about 6 hours.